Topical therapy is underused in patients with ulcerative colitis

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Abstract: The availability of new topical preparations for the treatment of left sided ulcerative colitis offers a therapy optimization for many patients. Rectal application of steroids and 5-aminosalicylic acid (5-ASA) is associated with fewer side effects and has a higher therapeutic efficacy in left-sided colitis as compared to a systemic therapy. Therefore, we were interested in the use of topical therapy in patients with ulcerative colitis. The key question was whether topical treatment is more frequently used than oral therapy in patients with proctitis and left sided colitis. Data of 800 patients of the Swiss IBD cohort study were analyzed. Sixteen percent of patients of the cohort had proctitis, 21% proctosigmoiditis and 41% pancolitis. Topical therapy with 5-ASA or corticosteroids was given in 26% of patients with proctitis, a combined systemic and topical treatment was given in 13%, whereas systemic treatment with 5-ASA without topical treatment was given in 29%. Proportion of topical drug use decreased with respect to disease extension from 39% for proctitis to 13.1% for pancolitis (P=0.001). Patients with severe colitis received a significantly higher dose of topical 5-ASA than patients in remission. Side effects of topical or systemic 5-ASA or budesonide treatment were less frequently seen compared to other medications. Topical treatment was frequently stopped over time. The quality of life was the same in patients with limited disease compared to patients with pancolitis. Topical treatment in proctitis patients was underused in Switzerland. Since topical treatment is safe and effective it should be used to a larger extend.

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Topical therapy is underused in patients with left sided colitis

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Abstract

The availability of new topical preparations for the treatment of left sided ulcerative colitis offers a therapy optimization for many patients. Rectal application of steroids and 5-aminosalicylic acid (5-ASA) is associated with fewer side effects and has a higher therapeutic efficacy in mild to moderate-active left-sided colitis as compared to a systemic therapy. It is recommended in international guidelines; however, especially with respect to topical therapy guidelines may not be followed regularly. We investigated the use of topical therapy in the Swiss National IBD cohort study (SIBDCS).

Sixteen percent of patients of the SIBDCS suffered from proctitis, 21% had procto-sigmoiditis and 41% had pancolitis. Topical therapy with 5-ASA or corticosteroids was given in only 23% of patients with proctitis, whereas a combined systemic and topical treatment was given in 11%. Systemic oral treatment with 5-ASA without topical treatment was given in 29%. A subgroup of 8% received immunomodulators or anti-TNF antibodies. Side effects of topical or systemic 5-ASA or budesonide treatment were less frequently reported as compared to other medications. Topical treatment was frequently stopped over the disease course and not used for maintenance of remission. The quality of life was the same in patients with limited disease compared to patients with pancolitis.

Topical treatment in proctitis patients was underused in the SIBDCS and not applied according to current guideline recommendations. Since topical treatment is safe and effective its use should be encouraged

Keywords:

Ulcerative colitis; topical therapy; rectal application; proctitis, quality of life

Introduction

Ulcerative colitis (UC) is a chronic relapsing inflammatory disorder of the colon and besides Crohn's disease (CD) one of the two major forms of inflammatory bowel disease (IBD). Its incidence in Europe is estimated to be around 5 to 25 new patients per 100.000 inhabitants per year. The etiology of UC remains unclear and subsequently medical therapies are not available that may completely cure the disease. The clinical presentation of UC is characterized by abdominal pain, diarrhea with or without hematochezia and mucosal ulcerations. UC is limited to the mucosa of the large intestine. It always involves the rectum and shows variable extension to the left sided or entire colon. 70% of the UC patients in population based studies exhibit only a proctitis/procto-sigmoiditis or left sided colitis. Only 30% will have extended disease (Solberg et al. 2009a). This may be different in a cohort such as the SIBDCS which includes 2/3 hospital treated patients having more severe of extensive disease.

In addition to the varying extend of the disease there is a wide variation in the severity of UC. Clinically mild disease is associated with less than four bowel movements per day, with or without bloody stools but without systemic manifestations. Blood tests in patients with mild disease are usually normal. Moderate disease has been defined as more than four bowel movements per day with minor systemic manifestations. Severe disease describes is attributed to patients with more than six bowel movements a day, fecal blood loss and systemic signs of inflammation. Classifications for disease severity show minor differences, however, the criteria for the discrimination of mild, moderate and severe disease remain more or less the same. An increased risk for the development of colorectal carcinoma (CRC) in UC patients with long lasting pancolitis has been described (Eaden 2004). This CRC risk appears to be reduced by sufficient anti-inflammatory medical therapy and by the achievement of mucosal healing. Proctitis appears not to be associated with increased CRC risk.

The basic treatment in mild to moderate UC is 5-aminosalicylic acid (5-ASA; mesalazine or mesalamine) irrespective of the disease localization. However, in patients with proctitis or left sided colitis topical application of 5-ASA as suppository, enema or foam preparation is more effective as compared to systemic treatment (Gionchetti, P., et al., Review article: treatment of mild to moderate ulcerative colitis and pouchitis. Aliment Pharmacol Ther, 2002. 16 Suppl 4: p. 13-9). Topically administrated steroids are superior to placebo in this situation, however, inferior if compared to topical 5-ASA (Marshall, J.K. and E.J. Irvine, Rectal corticosteroids versus alternative treatments in ulcerative colitis: a meta-analysis. Gut, 1997. 40(6): p. 775-81.; Campieri, M., et al., Efficacy of 5-aminosalicylic acid enemas versus hydrocortisone enemas in ulcerative colitis. Dig Dis Sci, 1987. 32(12 Suppl): p. 67S-70S). Therefore the treatment of choice in mild to moderate left-sided colitis is 5-ASA foams or enemas (Marshall, J.K. and E.J. Irvine, Rectal aminosalicylate therapy for distal ulcerative colitis: a meta-analysis. Aliment Pharmacol Ther, 1995. 9(3): p. 293-300.). During acute flares of the disease enemas are frequently less well tolerated due to their volume of up to 100 ml (Campieri, M., et al., 5-Aminosalicylic acid as enemas or suppositories in distal ulcerative colitis? J Clin Gastroenterol, 1988. 10(4): p. 406-9). As usually the rectum is affected by the most severe inflammation while containing the highest number of sensory nerves it is easily understandably by high volume enemas cause discomfort and urgency. Foam preparations are usually better tolerated and accepted by patients with acute flares of left sided colitis (Regueiro, M., et al., Medical management of left-sided ulcerative colitis and ulcerative proctitis: critical evaluation of therapeutic trials. Inflamm Bowel Dis, 2006. 12(10): p. 979-94.)

Compliance and patient acceptance is essential for the success of a rectal therapy (Katz S, Lichtenstein GR, Safdi MA. 5-ASA Dose-Response: Maximizing Efficacy and Adherence. Gastroenterol Hepatol (N Y). 2010;6(2 Suppl 3):1-16; Prantera C, Rizzi M. 5-ASA in ulcerative colitis: improving treatment compliance. World J Gastroenterol. 2009;15:4353-5. Kane SV, Brixner D, Rubin DT, Sewitch MJ. The challenge of compliance and persistence: focus on ulcerative colitis. J Manag Care Pharm. 2008;14:s2-12; Fernandez-Becker NQ, Moss AC. Improving delivery of aminosalicylates in ulcerative colitis: effect on patient outcomes Drugs. 2008;68:1089-103.) In general patients well accept to perform topical therapy if explained properly (Hawthorne AB, Rubin G, Ghosh S. Review article: medication non-adherence in ulcerative colitis--strategies to improve adherence with mesalazine and other maintenance therapies. Aliment Pharmacol Ther. 2008;27:1157-66; Kane SV. Systematic review: adherence issues in the treatment of ulcerative colitis. Aliment Pharmacol Ther. 2006;23:577-85.). It is not the case that a topical therapy per se is associated with lower adherence and compliance. Only in very severe disease application of topical therapy may cause pain and discomfort. Therefore, topical therapy may be paused during severe disease flares.

As mentioned foam preparations are better tolerated as compared to enemas (Marshall JK, Thabane M, Steinhart AH, Newman JR, Anand A, Irvine EJ. Rectal 5-aminosalicylic acid for induction of remission in ulcerative colitis. Cochrane Database Syst Rev. 2010;(1):CD004115.; James SL, Irving PM, Gearry RB, Gibson PR. Management of distal ulcerative colitis: frequently asked questions analysis. Intern Med J. 2008;38:114-9. Cortot A, Maetz D, Degoutte E, Delette O, Meunier P, Tan G, Cazals JB, Dewit O, Hebuterne X, Beorchia S, Grunberg B, Leprince E, D'Haens G, Forestier S, Idier I, Lémann M. Mesalamine foam enema versus mesalamine liquid enema in active left-sided ulcerative colitis. Am J Gastroenterol. 2008; 103:3106-14;

Pokrotnieks J, Marlicz K, Paradowski L, Margus B, Zaborowski P, Greinwald R. Efficacy and tolerability of mesalazine foam enema (Salofalk foam) for distal ulcerative colitis: a double-blind, randomized, placebo-controlled study. Aliment Pharmacol Ther. 2000; 14:1191-8). 5-ASA foam preparations have a similar distribution pattern as compared to enemas (Campieri M, Corbelli C, Gionchetti P, Brignola C, Belluzzi A, Di Febo G, Zagni P, Brunetti G, Miglioli M, Barbara L. Spread and distribution of 5-ASA colonic foam and 5-ASA enema in patients with ulcerative colitis. Dig Dis Sci. 1992; 37:1890-7.). 5-ASA suppositories in a dosage of 1g/day are the preferred therapy of mild to moderate proctitis (Marshall JK, Thabane M, Steinhart AH, Newman JR, Anand A, Irvine EJ. Rectal 5-aminosalicylic acid for induction of remission in ulcerative colitis. Cochrane Database Syst Rev. 2010;(1):CD004115.) A meta-analysis of 11 studies showed a median remission rate of 67% for rectal 5-ASA (as compared with 7 to 11% for placebo (Marshall JK, Irvine EJ. Rectal aminosalicylate therapy for distal ulcerative colitis: a meta-analysis. Aliment Pharmacol Ther. 1995; 9: 293-300.). A study by Eliakim and co-workers with a low volume rectal 5-ASA foam preparation showed remission rates of 78% in patients with mainly proctitis (Eliakim R, Tulassay Z, Kupcinskas L, Adamonis K, Pokrotnieks J, Bar-Meir S, Lavy A, Mueller R, Greinwald R, Chermesh I, Gross V; International Salofalk Foam Study Group. Clinical trial: randomized-controlled clinical study comparing the efficacy and safety of a low-volume vs. a high-volume mesalazine foam in active distal ulcerative colitis. Aliment Pharmacol Ther. 2007 ; 26: 1237-49.)

Topical steroids should be used for patients that are intolerant to 5-ASA. However, an additive therapy of topical 5-ASA and steroid may also be beneficial (Mulder CJ, Fockens P, Meijer JW, van der Heide H, Wiltink EH, Tytgat GN. Beclomethasone dipropionate (3 mg) versus 5-aminosalicylic acid (2

g) versus the combination of both (3 mg/2 g) as retention enemas in active ulcerative proctitis. Eur J Gastroenterol Hepatol. 1996;8:549-53.).

In moderate active distal colitis topical 5-ASA therapy in combination with oral 5-ASA therapy has proven to be highly effective (88% response after 6 weeks) (Safdi M, DeMicco M, Sninsky C, Banks P, Wruble L, Deren J, Koval G, Nichols T, Targan S, Fleishman C, Wiita B. A double-blind comparison of oral versus rectal mesalamine versus combination therapy in the treatment of distal ulcerative colitis. Am J Gastroenterol. 1997; 92: 1867-71.) A meta-analysis of 33 studies showed that topical 5-ASA is more effective as compared to topical conventional steroids or budesonide (Marshall JK, Thabane M, Steinhart AH, Newman JR, Anand A, Irvine EJ. Rectal 5-aminosalicylic acid for induction of remission in ulcerative colitis. Cochrane Database Syst Rev. 2010;(1):CD004115.; Marshall JK, Irvine EJ. Rectal corticosteroids versus alternative treatments in ulcerative colitis: a meta-analysis. Gut. 1997; 40: 775-81. Marshall JK, Irvine EJ. Putting rectal 5-aminosalicylic acid in its place: the role in distal ulcerative colitis. Am J Gastroenterol. 2000;95: 1628-36.)

Remission also can be maintained by topical treatment of at least two years duration Katz S, Lichtenstein GR, Safdi MA. 5-ASA Dose-Response: Maximizing Efficacy and Adherence. Gastroenterol Hepatol (N Y). 2010;6(2 Suppl 3):1-16; Prantera C, Rizzi M. 5-ASA in ulcerative colitis: improving treatment compliance. World J Gastroenterol. 2009;15:4353-5. Kane SV, Brixner D, Rubin DT, Sewitch MJ. The challenge of compliance and persistence: focus on ulcerative colitis. J Manag Care Pharm. 2008;14:s2-12; Rogler G. Medical management of ulcerative colitis. Dig Dis. 2009;27:542-9.

Travis SP, Stange EF, Lémann M, Oresland T, Bemelman WA, Chowers Y, Colombel JF, D'Haens G, Ghosh S, Marteau P, Kruis W, Mortensen NJ, Penninckx F, Gassull M; for the European Crohn's and Colitis Organisation (ECCO). European evidence-based Consensus on the management of ulcerative colitis: Current management. Crohns Colitis. 2008;2:24-62.). For maintenance 3 g of 5-ASA total per week are recommended.

A topical therapy in distal UC has several advantages. The majority of patients has a distal disease type (Rogler G. Medical management of ulcerative colitis. Dig Dis. 2009;27:542-9. Lakatos PL, Lakatos L. Ulcerative proctitis: a review of pharmacotherapy and management. Expert Opin Pharmacother. 2008;9:741-9). Thus a topical therapy should be applied in the majority of patients with UC as the success rate is higher as compared to oral therapy and side effects are fewer. However, ther are reports of an underuse of topical therapies despite guideline recommendations (Reddy SI, Friedman S, Telford JJ, Strate L, Ookubo R, Banks PA. Are patients with inflammatory bowel disease receiving optimal care? Am J Gastroenterol. 2005;100:1357-61.)

The aim of this study was to investigate the use of topical and systemic therapies in patients with ulcerative colitis of the Swiss IBD cohort study

Methods

Data of the Swiss National Cohort study were used to perform this study. The cohort is described elsewhere (Valery you may know the best reference). The aim of the study was the characterization of the use of topical versus oral therapies in UC patients within the Swiss IBD cohort. We performed a cross-sectional (transversal) analysis of data of the Swiss IBD cohort. Furthermore a longitudinal data analysis was done in a subgroup of patients where the data is available.

Treatments of interest were classified as follows: systemic (Oral 5-ASA, budesonide), topical (topical 5-ASA, topical Steroids), combination of both systemic and topical, immunomodulators (Azathioprine, 6-Mercaptopurine, Methotrexate), anti-TNF alpha antibodies (Infliximab, Adalimumab, Certolizumab-pegol), other therapies (e.g. antiobiotics, steroids), and no therapy at all.

Self-completed SF36 quality of life questionnaires were used to assess life conditions of patients at the different stages of follow-up.

Statistics

We used chi-squared test to estimate differences between independent groups for categorical variables, and Kruskall-Wallis one way analysis of variance to compare medians of continuous variables among independent groups. A level of 5% was considered to be statistically significant.

Results

General description of the study population

Among 1961 patients with IBD enrolled in the Swiss IBD Cohort between 2006 and 2011, 800 (40.8%) were originally diagnosed with UC. During follow-up, 10 patients experienced a change of diagnosis, either to CD or to indeterminate colitis. Therefore, a total of 790 patients were included in this study. 538 of those patients (68.1%) completed a 1st-year follow-up, 381 (48.2%) completed a 2nd-year follow-up, and 263 (33.3%) completed a 3rd-year follow-up.

The baseline clinical characteristics of the study population are presented in Table 1. Little more than the half were males (N=429), with mean age of 44.3 years (SD 14.5, range 16 to 85), and a mean disease duration of almost 11 years (SD 8.7, range 0 to 49).

Males more often had an extensive colitis (44.3% vs 36%) and women a proctosigmoiditis or proctitis. (23.3% vs 18.0%, respectively 18.8% vs 14.2%, p=0.025).

Among the 526 patients that were followed for at least one year and for which disease location was documented, 74 (14.1%) experienced a regression of the disease extension, 40 (7.6%) an expansion of the disease extension.

Medication

We analyzed the use of medication for all 773 patients with known disease location according to the subgroups of patients with different intestinal involvement. Topical treatment was mainly used in patients with proctitis and proctosigmoiditis. Twenty-nine percent of the patients were exclusively orally treated with 5-ASA, whereas topical therapy was given in 25.6% of patients with proctitis. A fraction of patients (13%) received oral and topical treatment simultaneously. A total of 50.5% of proctitis patients were treated exclusively with oral or iv medication. The use of systemic drugs was less frequent for proctitis (29.5%) than for the other disease locations (p=0.009). (Table I)

In patients with proctosigmoiditis a total 80% of patients were treated systemically. Proportion of topical drug use decreased with respect to disease extension from 24% for proctosigmoiditis to 13.1% for pancolitis (p=0.001) (Figure 1).

Interestingly the use of immunomodulators differed significantly between the groups. They were most frequently used in patients with left sided colitis, followed by patients with a pancolitis (p=0.001). However, 4.7% of patients with proctitis and 12.4% of patients with proctosigmoiditis were treated with immunomodulators (Table I).

The use of anti TNF antibodies varied between the groups. Six percent of patients with pancolitis and left-sided colitis were treated with this medication compared to 3.1 percent of patient with proctitis but the difference between all groups was not found to be statistically significant (p=0.464)(Table I).

More than one third of all patients with ulcerative colitis (38.9%, N=301) were treated with systemic 5-ASA without topical treatment, whereas only 9.6% (N=74) were exclusively treated with topical drugs, and 1 out of 10 (N=86) were treated with a combination of systemic and topical medication. Topical steroids or budesonide were relatively infrequently used in the Swiss IBD cohort, whereas the mainstay of topical therapy consisted of topical 5-ASA formulations.

Side effects of medical treatment

Treatment with 5-ASA and budesonide (orally or topically) was significantly less frequently associated with side effects compared to immunomodulator or anti-TNF-alpha antibody treatment ($p<0.001$) . Oral 5-ASA was the most common therapy (336/790, 42.5%), and patients experienced side effects in 13.1% of the cases. Most common side effects of oral 5-ASA treatment were asthma, skin rash, interstitial nephritis, diarrhea and pancreatitis. Topical 5-ASA or topical steroids were given in a total 334 cases (42.3%), while 65 patients (8.2%) were treated by both. Most common side effects of topical 5-ASA treatment were painful application of treatment, diarrhea due to intolernance, and skin rash. Side effects occurred in 25 cases out of 334 (7.5%) patients treated with topical therapies. Immunomodulators were given in 239 out of 790 cases (30.3%), leading to 116 occurrences of side effects (48.5%). Side effects for anti-TNF alpha antibody treatment were described in 24% of the cases.

Change of treatment

We were interested how long patients will remain on a topical treatment in contrast to a systemic treatment. For patients under a topical therapy, change of medication occurs more frequently than in those under a systemic therapy (up to more than 50% of the cases). Change is made generally either to a fully systemic treatment (19 cases out of 58, 32.7%), or either to an additional systemic drug (13 out of 58, 22.4%). For patients under a systemic-topical combined treatment, change of drug is mainly an interruption of the topical treatment (42 cases out of 69, 60.9%). For patients under systemic drugs only, at least 70% do not have to change their therapy at any stage of the follow-up. When they have to, in more than 30% of the cases an additional topical drug is given (36 cases out of 118 over all period), while only 14% change to a fully topical treatment (16 out of 118)(Table 4).

Quality of life

We were interested whether the quality of life was different in patients with limited disease in contrast to patients with pancolitis. The physical and mental components were measured by the SF 36 questionnaire. Patients with limited disease had similar scores compared to patients with pancolitis. Mental score seemed to be lower in proctosigmoiditis patients than in others, at follow-up 2 ($p=0.036$)(Table 5).

Discussion

In this study we investigated the use of rectal therapies with 5-ASA and steroids in the Swiss national IBD cohort. Topical treatment was most frequently used in patients with proctitis. The proportion of topical drug use decreased significantly with respect to an increase of intestinal involvement. The data of the Swiss national cohort study show that 57% of the patients had a colitis limited to the rectum or to the left colon. Our study revealed that oral 5-ASA was more frequently given in patients with proctitis than rectal formulations. Several studies showed the efficacy of rectal treatment with suppositories at a dosage of 1 g /day(James SL, Marshall JK, Casellas F, D'Arienzo A). Rectal foams can be alternatively used. Rectal 5-ASA applications achieve remission rates in the literature around 67% (Marshall JK). In another study 78% of patients came into remission using a 5-ASA foam (Eliakim R). Topical steroids should be used in patients intolerant or refractory to 5-ASA products. They can be added to a 5-ASA treatment (Mulder CJ).

In patients with proctosigmoiditis 5-ASA therapy has also been shown to be effective at a dosage of 2 g/d (Safdi M). Interestingly it was demonstrated that the combination of rectal and oral 5-ASA increased the efficiency of treatment (Safdi M). After a treatment period of 6 weeks with 2.4 g of oral 5-ASA 33% had no fecal blood whereas 54% of rectally treated patients and 88% of patients treated with an oral rectal combination treatment did respond to the therapy.

It is unclear why the frequency of rectal therapy is relatively low in Switzerland. The data in the literature clearly show a superiority of rectal treatment compared to oral treatment in patients with proctitis and proctosigmoiditis. We assume that most Swiss gastroenterologists know of these details, therefore other factors seem to influence the treatment decisions. In the follow up studies in this paper we realized that topical treatment was frequently stopped and not used as a maintenance treatment. We speculate that patients prefer to take capsules instead of suppositories, enemas or

rectal foams. To overcome this fact, better information and teaching of our patients may be helpful. Even in the maintenance of remission rectal 5-ASA formulations are helpful in patients with proctitis or proctosigmoiditis. The patients should be encouraged to maintain the treatment with a minimal weekly dose of 3g of 5-ASA (D'Albasio G, Piodi LP). [3-64-74-76-98-118-113-6]

In our study rectal 5-ASA products were significantly more frequently given than steroids. In one study the efficacy of budesonide versus mesalazine enemas has been compared in patients with left-sided ulcerative colitis. Clinical remission at week 4 was achieved in 63.5% of budesonide and 77.2% of mesalazine treated patients ($p<0.05$) (Hartmann). Furthermore, a meta-analysis showed a higher efficiency of rectal 5-ASA treatments compared to topical steroids (Marshall JK, Marshall JK, Marshall JK). However, the combination of rectal steroids and 5-ASAs seems to be beneficial (Mulder CJ).

In our cohort only a minority of patients with pancolitis received rectal therapy. Since urgency and high stool frequency are related to a rectal involvement a proportion of these patients may profit of an additional rectal therapy. A study proofed the efficacy of rectal therapy in patients with mild to moderate pancolitis in the combination with oral 5-ASA (Marteau P).

No difference of quality of life was found in patients regarding to their intestinal involvement. This indicates that patients with only limited disease may suffer as much as patients with pancolitis. Therefore, patients with only a limited intestinal involvement will possibly profit of an optimization of their treatment regarding their quality of life.

Rectal treatment, however, has its limitations. A subgroup of patients is unable to retain the enema. Therefore, rectal foams have been developed. The comparison between mesalamine foams versus mesalamine liquid enema in patients with active left-sided ulcerative colitis showed a not significant lower remission rate induced by the foam formulations. (Cortot). Despite of the fact that topical treatment may be more efficient than oral treatment a subgroup of patients does not feel comfortable to do the therapy on a daily basis. Therefore, there have been attempts for other galenic formulations to avoid the rectal administration. A new budesonide MMX extended-release tablet has been investigated in a trial that showed that 47% of patients reached a CAI reduction by 50% in contrast to placebo (33%). (D'haens).

In this study, the frequency of side effects in patients treated with topically or orally given 5-ASA products was low compared to those treated with immunomodulators or anti-TNF-antibodies. This is in accordance to other papers (Ford).

Due to the fact that university hospitals included the majority of the patients in this cohort, there may be a bias leading to an elevated frequency of pancolitis patients (40.5%). In another cohort only 22% of patients with ulcerative colitis suffered from pancolitis (Lakatos). Furthermore, the disease activity of our patients might be higher than in a population based cohort.

In summary, there are several advantages of rectal treatment with 5-ASA or topical steroids in patients with ulcerative colitis. This includes a high therapeutic efficacy and low side effects. Due to these advantages physicians should encourage their patients to use rectal therapies. With the increasing number of rectal formulations on the market (suppositories, enema, low volume foam) most patients with ulcerative colitis will find an agreeable product.

	Total, N (%)
Patients	
Males	429 (54.3)
Age, y	
Mean (SD, range)	44.3 (14.5, 16-85)
Age at 1st symptoms, y	
Mean (SD, range)	32.1 (13.1, 3-78)
Disease duration, y	
Mean (SD, range)	10.8 (8.7, 0-49)
Current disease location	
Pancolitis	320 (40.5)
Left Sided Colitis	163 (20.6)
Proctosigmoiditis	161 (20.4)
Proctitis	129 (16.3)
Unknown or unclear	17 (2.2)

Table 1: Baseline characteristics of study population.

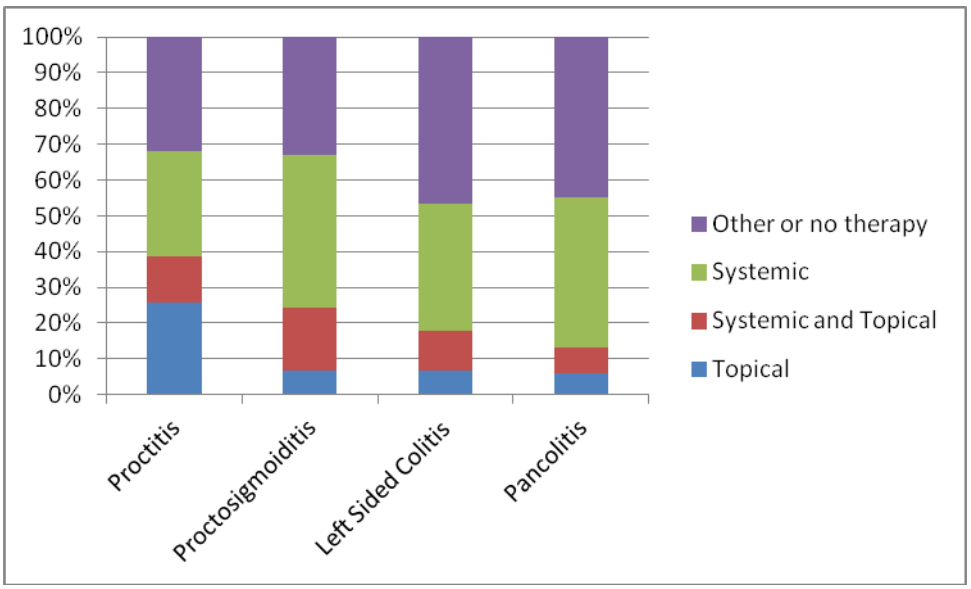

Figure 1: Medication according to disease location.

	Proctitis N (%)	Proctosigmoiditis N (%)	Left-sided colitis N (%)	Pancolitis N (%)	total N (%)
Location, N(%)	129(16.7)	161(20.8)	163(21.1)	320(41.4)	773
Systemic					
Oral 5-ASA	37(28.7)	64(39.7)	57(35.0)	127(39.7)	285(36.9)
Budesonide	0(0.0)	2(1.2)	1(0.6)	5(1.6)	8(1.0)
Oral 5-ASA, Budesonide	1(0.8)	3(1.9)	0(0.0)	3(0.9)	7(0.9)
Total systemic	38(29.5)	69(42.8)	58(35.6)	135(42.2)	301(38.9)
Topical					
Topical 5-ASA	30(23.3)	8(5.0)	7(4.3)	15(4.7)	60(7.8)
Topical Steroids	3(2.3)	3(1.9)	2(1.2)	3(0.9)	11(1.4)
Topical 5-ASA, Topical Steroids	0(0.0)	0(0.0)	2(1.2)	1(0.3)	3(0.4)
Total topical	33(25.6)	11(16.9)	11(6.7)	19(5.9)	74(9.6)
Systemic and Topical					
Oral 5-ASA, Topical 5-ASA	14(10.8)	23(14.3)	13(8.0)	18(5.6)	68(8.8)
Oral 5-ASA, Topical Steroids	2(1.6)	3(1.9)	4(2.5)	4(1.3)	13(1.7)
Oral 5-ASA, Topical 5-ASA, Budesonide	0(0.0)	1(0.6)	0(0.0)	0(0.0)	1(0.1)
Oral 5-ASA, Topical 5-ASA, Topical Steroids	1(0.8)	1(0.6)	1(0.6)	0(0.0)	3(0.4)
Oral 5-ASA, Budesonide, Topical Steroids	0(0.0)	0(0.0)	0(0.0)	1(0.3)	1(0.1)
Total systemic and topical	17(13.2)	28(17.4)	18(11.1)	23(7.2)	86(11.1)
Immunomodulators	6(4.7)	20(12.4)	34(20.9)	45(14.0)	105(13.6)
Anti-TNF alphas	4(3.1)	12(7.4)	10(6.1)	19(6.0)	45(5.8)
Other therapy	17(13.2)	14(8.7)	14(8.6)	32(10.0)	77(9.9)
No therapy	14(10.8)	7(4.4)	18(11.0)	47(14.7)	86(11.1)

Table 2: Medication for all 773UC patients with known disease location.

Table 2 shows medication for all 773 patients with known disease location. More than one third of the patients (38.9%, N=301) were treated with only systemic anti-inflammatory drugs or budesonide, 9.6% (N=74) were treated with topical drugs, and 1 out of 10 (N=86) were treated with a combination of systemic and topical medication. Immunomodulating drugs were used in 105 cases (13.6%), biological agents in 45 cases (5.8%).

Side effects

	Past therapy	%	Side effect	%
Oral 5-ASA	336	42.5	44	13.1
Budesonide	74	9.4	1	1.4
Topical 5-ASA	250	31.6	18	7.2
Topical Steroids	149	18.9	7	4.7
Immunomodulators	239	30.3	116	48.5
Anti-TNF alphas	96	12.2	23	24.0

Table 3: Past therapies and side effects for stopped therapies

Table 3 shows past treatment, used by UC patients, as well as reported side effects that led to therapy cessation. Oral 5-ASA was the most common past therapy (336/790, 42.5%), and patients experienced side effects in 13.1% of the cases. Topical 5-ASA or Topical Steroids were given in a total 334 cases (42.3%), while 65 patients (8.2%) were treated by both. Combined side effects occurrence for topical therapy is 25 cases out of 334 (7.5%). Immunomodulator drugs were given in 239 out of 790 cases (30.3%), leading to 116 occurences of side effects (48.5%).

Change of treatment

From Enrollment to Follow-up 1:

Enroll/FUp1	Systemic	Topical	Syst&Topic	Immunomod	Anti-TNF	Other	No therapy
Systemic	142 (71.0%)	10	16	15	2	3	12
Topical	10	25 (46.3%)	9	3	1	2	4
Syst&Topic	28	4	25 (37.9%)	1	1	3	4

From Follow-up 1 to Follow-up 2:

FUp1/FUp2	Systemic	Topical	Syst&Topic	Immunomod	Anti-TNF	Other	No therapy
Systemic	90 (70.3%)	4	12	9	5	3	5
Topical	8	19 (47.5%)	3	2	2	5	1
Syst&Topic	7	4	20 (54.1%)	2	1	3	0

From Follow-up 2 to Follow-up 3:

FUp2/FUp3	Systemic	Topical	Syst&Topic	Immunomod	Anti-TNF	Other	No therapy
Systemic	57 (72.2%)	2	8	4	3	4	1
Topical	1	11 (57.9%)	1	1	1	1	3
Syst&Topic	7	2	8 (42.1%)	0	0	2	0

Table 4: Change of medication between different stages of follow-up

Table 4 shows the change of medication between different stages of follow-up. Overall number of patients is decreasing since not every patient has filled all yearly follow-ups. For patients under systemic drugs only, we observed a total of 118 treatment switches over the whole period, which means that at least 70% do not have to change their therapy at any stage of the follow-up. When they have to, in more than 30% of the cases an additional topical drug is given (36 cases out of 118 over all period), while only 14% change to a fully topical treatment (16 out of 118). For patients under a topical therapy, change of medication occurs in 58 total cases over the whole period (more than 50% of the cases)., which is more often than the systemic drugs group. Change is made generally either to a fully systemic treatment (19 cases out of 58, 32.7%), or either to an additional systemic drug (13 out of 58, 22.4%). For patients under a systemic-topical combined treatment, change of drug is mainly an interruption of the topical treatment (42 cases out of 69 total switches were made towards a systemic drug only, which represents more than 60% of the cases).

Quality of life

	Proctitis	**Proctosigmoiditis**	**Left Sided colitis**	**Pancolitis**	
Enrollment					
Physical	53.0	51.1	51.2	51.3	P=0.150
Mental	47.3	46.0	46.7	48.2	P=0.327
Follow-up 1					
Physical	55.2	52.9	50.2	52.8	P=0.057
Mental	48.9	48.7	48.6	51.2	P=0.825
Follow-up 2					
Physical	55.1	51.9	53.4	54.2	P=0.063
Mental	49.0	46.4	49.9	50.7	P=0.036
Follow-up 3					
Physical	54.7	51.5	51.6	56.0	P=0.125
Mental	51.2	48.4	50.6	50.7	P=0.808

Table 5: Median of SF36 Physical and Mental component scores according to disease location for different times of follow-up.

Table 5 summarizes the median of both Physical and Mental component scores of the SF36 questionnaire at different times of follow-up and according to disease location. Mental score seems to be lower in proctosigmoiditis patients than in others, at follow-up 2 (p=0.036). No statistical difference was found, except for Mental score at follow-up 2.

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